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(56) Documents Cited
EP 0367140 A2 WO 92/02136 A1
Chemical Abstract 118(17):163281m & JP04352703 A2
Chemical Abstracts 115(21):226183s and JPO3133906
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CN86105233 A Chemical Abstracts 104(11): 83820g
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(54) **Insect repellent compositions**

(57) An insect repellent composition contains one or both isomers of p-menthane-3,8-diol which has been extracted from a natural oil or synthesised chemically, and a carrier.

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INSECT REPELLENT COMPOSITIONS

This invention relates to insect repellent compositions.

Diethyl toluamide is a widely used insect repellent. There are also a number of natural products which show insect repellency to a greater or lesser degree. Among these is citronella oil which is obtained from certain grasses. Also, certain species of Eucalyptus contain a natural product in their leaves which displays insect repellent properties.

We have made an investigation of these naturally occurring products to try to isolate and identify the active material which gives rise to the insect repellent properties. After considerable work, we have found that the active material is p-menthane-3,8-diol. The material can be extracted and purified from its naturally occurring sources. Alternatively, it can be synthesised chemically as described, for example, by Zimmerman and English in J.A.C.S. 75 (1953) pp 2367-2370.

In one aspect, the present invention provides an insect repellent composition which comprises p-menthane-3,8-diol and a physiologically acceptable carrier therefor, the said diol having been extracted from a natural oil or having been synthesised chemically.

It is to be understood that the invention does not extend to the use, as an insect repellent, of the p-menthane

-3,8-diol containing natural oils themselves. Rather, in the compositions of the invention, any naturally occurring p-menthane-3,8-diol (hereinafter abbreviated to "PMD") has been extracted from a natural source and thus has been at least partly separated from other substances in admixture with which it naturally occurs. The PMD can be very pure or it can still contain other materials from its source.

We have further investigated PMD and its insect repellency properties (particularly towards mosquitoes). PMD can exist in two geometric isomeric forms, namely the cis and the trans isomers. We have separated PMD into its component isomers and have tested each, and mixtures, to determine their insect repellent properties. We have found that the isomers display different insect repellent properties and, in particular, that the trans isomer initially has the better repellency, whereas the cis isomer has a longer lasting effect.

According to a further aspect of the invention, there is provided an insect repellent composition which comprises only one of the isomers of PMD, with a carrier therefor.

In accordance with a highly preferred feature of the invention, the relative quantities of cis and trans PMD isomers can be adjusted to provide the desired effect. For example, for high repellency immediately after application, the ratio cis:trans should be low (i.e. there is more trans than cis). For a long lasting effect, however, the cis:trans ratio should be high (more cis than trans).

The invention thus includes an insect repellent composition comprising a mixture of the cis and trans isomers of PDG, wherein the cis:trans ratio has been chosen to provide the desired insect repellency property.

These compositions can be made by mixing previously separated PDG isomers in the appropriate ratio, or by adjusting the ratio in a mixture of naturally occurring or synthetic source.

We have found that, for general purposes, the range of cis:trans ratios will be (by weight) from about 1.5:1 to about 6:1. The best range is from about 2:1 to about 3:1, with 2.5:1 being most preferred.

The invention thus includes an insect repellent composition which comprises the cis and trans isomers of PDG in a weight of cis:trans from 2:1 to 3:1, with a carrier therefor.

The compositions of the invention have been described above comprising a carrier. It is to be understood that the invention also encompasses the use of PDG and of its isomers (individually or in admixture) for insect repellency purposes with or without a carrier.

For normal use, the compositions of the invention will be formulated as sprayable liquids (e.g. solutions of PDG in suitable solvents such as alcohols), pressurised aerosols, lotions, creams, roll-ons or solid sticks, although other formulations can of course be used. It will be well understood by those skilled in the art as to how these formulations are made.

In order that the invention can be more fully understood, the following Examples are given by way of illustration only.

Example 1

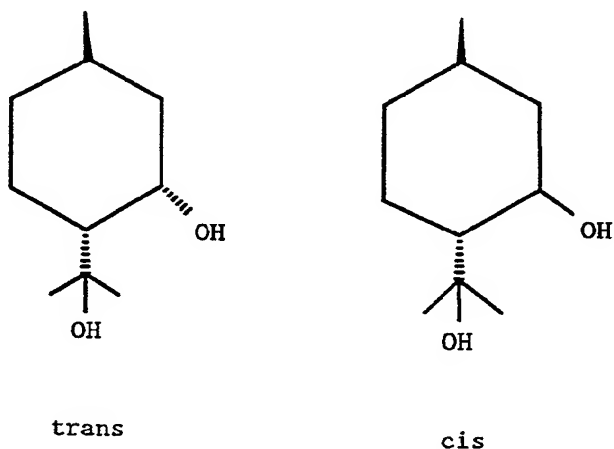
Separation of the isomers of PMD

PMD was synthesised as described in the literature from citronellal by reaction with 5% sulphuric acid. The product was chromatographed on a silica gel column, eluting with 9:1 cyclohexane-ethyl acetate (200ml), then with an equal amount of 4:1 of the same mixture. Evaporation of the appropriate fractions (as determined by thin layer chromatography) yielded two products. ¹³CNMR spectrum of the fractions confirmed them as the pure cis and trans isomers of p-menthane-3,8-diol along with a little

cyclohexane (the chromatography solvent). The physical properties of these isomers were:

1. Colourless, very viscous, glycerol-like liquid with a faint citrus odour
2. Limited solubility in water but miscible with ethanol, ether and (warm) petrol solvents
3. Boiling point between 129-142°C at 5mm Hg
4. Density less than 1
5. Not light sensitive and temperature stability is high.

The chemical structures were:



Example 2

Repellency Tests

In order to establish the most efficient mix of isomers for final formulation, we undertook repellency testing using human volunteers and live hungry female mosquitos.

Test Procedure

Both right and left forearms of human volunteers were washed with 2ml of industrial alcohol. The right forearm was used as a control and the left forearm for testing. An assistant wearing a fresh pair of rubber gloves

on each occasion applied the test material to the left forearm in the quantity described. The control arm was first introduced into a cage of hungry, mainly female mosquitoes. The number of mosquitoes probing at 45 seconds was counted. The mosquitoes were then shaken off and the arm withdrawn (the mosquitoes did not have sufficient time to actually feed and become satiated). The test arm was then introduced and the procedure repeated. The test arm was evaluated every hour for the test period and the control arm was retested at the end of the period to confirm that biting drive remained high.

We undertook the following experiments to compare the efficacy and longevity of each of the isomers:

1. Minimum effective dose

After initial control readings on both untreated arms, 0.04 ml of a 17.9% solution of the pure cis isomer in ethanol was applied and tested.

Incremental increases were applied until total repellency was achieved. Hourly testing was then carried out to measure the decay of repellent action. The same procedure was followed with a 7.4% solution of the trans isomer.

Results:

The total dose of cis isomer required to just achieve full repellency was 0.12ml of 17.9% solution or 21.5mg. Repellency was 50% at 1 hour and 11% at 2 hours. The total dose of trans isomer required to just achieve full repellency was 0.3ml of 7.4% solution or 22.2mg. Repellency was lost after 1 hour.

2. Longevity of action

We took equal quantities of the cis and trans isomers being 0.75ml of 17.9% cis in ethanol and 1.8ml of 7.4% trans in ethanol, giving the equivalent of 130mg of each isomer for each test. This was considered to be the appropriate amount

that would be applied in practice by an individual wishing to apply repellent for protection.

Results:

<u>Time</u> (hrs)	<u>% Repellency against control</u>		<u>Control no. of bites</u>	
	<u>Cis</u>	<u>Trans</u>	<u>Cis</u>	<u>Trans</u>
0	91.3	97.1	30	34
1	91.3	76.5		
2	85.5	70.6		
3	76.8	41.2		
4	56.5	29.7	39	38

From these results, it can be seen that although the cis isomer had some initial repellency, the trans isomer was even better. The cis clearly outlasted the trans, however, in longevity of action.

We therefore concluded that a cis:trans ratio in the region of between 2:1 and 3:1 would prove the best repellent for practical use, combining high initial efficacy with the longest lasting action.

Optimum Concentration Formulation

Having decided upon the best cis:trans ratio, we looked at the highest concentration of active ingredient that could be achieved in a practical preparation. Encouraged by the lack of any evidence of dermal toxicity in an initial experiment and with the known safe toxicity profile of Eucalyptus oil derivatives over many years, we felt that a high concentration was achievable. Because of the physical properties and requirements for dispersal as a spray, we felt that a 50% solution in ethanol should be tested.

We proceeded to test the efficacy of this 50% concentrate of a 2.5:1 cis:trans mixture of p-menthane-3,8-diol in alcohol. We tested against 2 different strains of mosquito, (Anopheles stephensi and Aedes aegypti) noted for their different biting patterns vectors respectively of the infectious agents of malaria and yellow fever, and against

the sandfly (Phlebotomus sp.) vectors of Leishmaniasis infection. We achieved 100% repellency against all types for at least 6 hours and in some cases 8 hours.

Example 3

As previously stated, our tests have used a 50% concentration of the 2.5:1 cis:trans mixture in ethanol for pump spray application. This same mixture is effective in butane pressurised aerosols, lotions, roll-ons, solid sticks, gels etc.

CLAIMS:

1. An insect repellent composition which comprises p-menthane-3,8-diol and a carrier therefor, the said diol having been extracted from a natural oil or having been synthesised chemically.
2. An insect repellent composition which comprises only one of the isomers of p-menthane-3,8-diol.
3. An insect repellent composition which comprises a mixture of the cis and trans isomers of p-menthane-3,8-diol, the cis:trans ratio having been chosen to provide the desired insect repellency property.
4. A method of making an insect repellent composition which comprises providing a mixture of the cis and trans isomers of p-menthane-3,8-diol in a ratio predetermined to provide the desired insect repellency property.
5. A composition according to claim 1 or 3 wherein the cis:trans ratio is from 2:1 to 3:1 by weight.
6. A composition according to any of claims 1,2,3 or 5, which comprises an alcohol as a carrier for the p-menthane-3,8-diol.
7. A composition according to claim 6, wherein the p-menthane-3,8-diol is in solution in ethanol.
8. A composition according to claim 7, wherein the solution is 50% by weight p-menthane-3,8-diol.
9. A composition according to claim 6,7 or 8, which is in a spray container.

10. A formulation of a composition as claimed in any of claims 1,2,3 or 5 to 8, in the form of a sprayable solution, an aerosol, a lotion, roll-on, solid stick or gel.

11. A formulation according to claim 10 for repelling mosquitoes.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

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Relevant Technical Fields

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P N DAVEY

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13 DECEMBER 93

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: CAS ONLINE

Documents considered relevant following a search in respect of Claims :-
1-11

Categories of documents

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|---|---|
| X: Document indicating lack of novelty or of inventive step. | P: Document published on or after the declared priority date but before the filing date of the present application. |
| Y: Document indicating lack of inventive step if combined with one or more other documents of the same category. | E: Patent document published on or after, but with priority date earlier than, the filing date of the present application. |
| A: Document indicating technological background and/or state of the art. | &: Member of the same patent family; corresponding document. |

Category	Identity of document and relevant passages	Relevant to claim(s)
X	WO 92/02136 A1 (R AND C PRODUCTS) see eg pages 17-18	1,7,9-11 at least
X	EP 0367140 A2 (TAKIRON) see eg Examples 1-5	1-5, 11 at least
X	Chemical Abstracts 118(7): 163281m and JP 04352703 A2 (NIPPON KAYAKU), see abstract	1 at least
X	Chemical Abstracts 115(21): 226183s and JP 03133906 A2 (NIPPON KAYAKU), see abstract	1, 10 at least
X	Chemical Abstracts 108(25): 217808c and CN 86105233 A (CHEMICAL FACTORY OF BEAUTY ARTICLES) see abstract	1, 11 at least
X	Chemical Abstracts 104(11): 83820g and JP 60199804 A2 (NIPPON KAYAKU) see abstract	1 at least

Databases:The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).